application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

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CAM:sd
Enclosures: Marked-up Version of Specification and Claims
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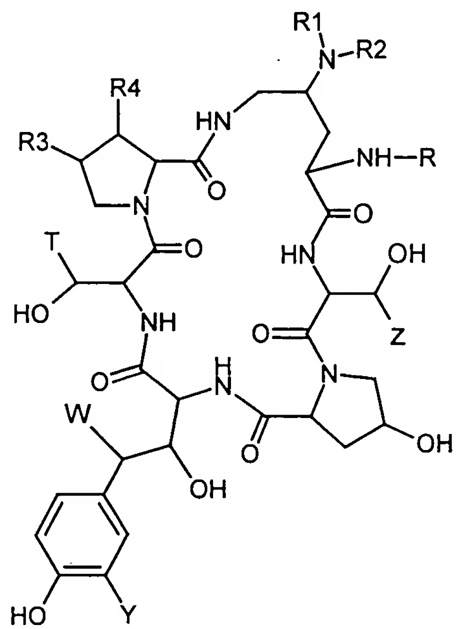
New derivatives of echinocandine, their preparation process and their use as antifungals.

--This application is a 371 of PCT/FR00/01569 filed June 8, 2000.--

The present invention relates to new derivatives of echinocandine, their preparation process and their use as antifungals.

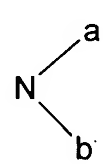
A subject of the invention is in all the possible isomer forms as well as their mixtures, the compounds of formula (I):



(I)

in which

either R_1 and R_2 identical to or different from one another, represent a hydrogen atom, a hydroxyl radical, a linear, branched or cyclic alkyl radical containing up to 8 carbon atoms optionally interrupted by an oxygen atom optionally substituted by a halogen atom, an OH radical, an



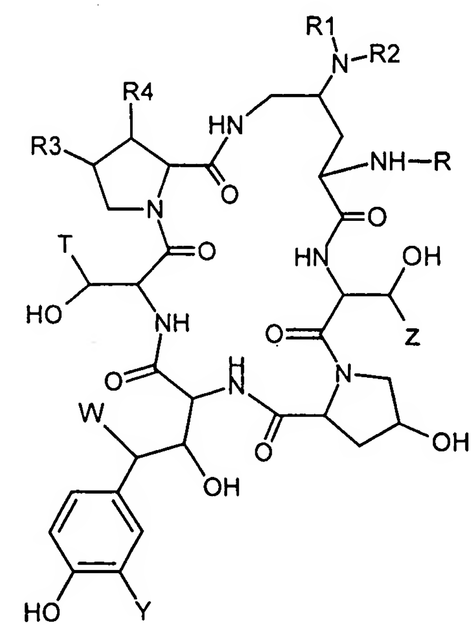
radical, a and b identical to or different from one another, representing a hydrogen atom or an alkyl radical containing up to 8 carbon atoms, a and b can optionally form with the nitrogen atom a heterocycle optionally containing one or more

MARKED-UP VERSION OF CLAIMS

Our Ref.: 146.1376

A compound selected from the group consisting of

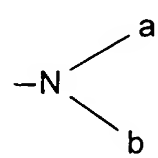
1) ~~In~~ all possible isomeric forms and ~~as well as~~ their mixtures of a ~~the~~ compound~~s~~ of the formula ~~(I).~~



(I)

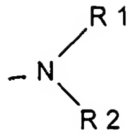
wherein ~~in which~~

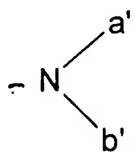
either R_1 and R_2 are individually selected from the group consisting of ~~identical to or different from one another, represent a~~ hydrogen ~~atom~~, ~~a~~ hydroxyl ~~radical~~, alkyl and ~~a linear, branched or~~ cycl~~ic~~ alkyl ~~radical containing~~ of up to 8 carbon atoms optionally interrupted by ~~an~~ oxygen ~~atom~~ and optionally substituted by a member selected from the group consisting of ~~a~~ halogen ~~atom~~,

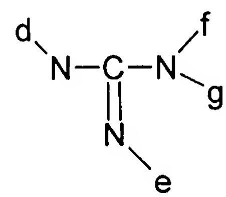
~~an~~ OH ~~radical~~, and ~~an~~  ra~~dical~~, a and b

are individually ~~identical to or different from one another~~, ~~representing a~~ hydrogen ~~atom~~ or ~~an~~ alkyl ~~radical containing~~ of ~~up~~ to 8 carbon atoms or a and b can optionally form with the nitrogen atom a heterocycle optionally containing at least one ~~or more~~ additional heteroatom~~s~~,

or R_1 forms with the endocyclic carbon atom

carrying ~~the~~  ~~radical~~ a double bond and ~~or~~ R2 ~~represents an~~ is -XRa ~~radical~~, X ~~representing an~~ is selected from the group consisting of oxygen, ~~atom or an~~ -NH- or -N-alkyl ~~radical containing up~~ of 1 to 8 carbon atoms and Ra ~~represents a~~ is hydrogen ~~atom~~, ~~a linear, branched or~~ alkyl cyclo-alkyl ~~radical containing~~ of up to 8 carbon atoms optionally substituted by at least one ~~or more~~ member of the group consisting of halogen ~~atoms~~, ~~by one or more~~ -OH, -CO_2H, -CO_2alk, and ~~radicals, by an~~



~~radical~~, a' and b' ~~representing a~~ are hydrogen ~~atom, an~~ or alkyl ~~radical containing up~~ of 1 to 8 carbon atoms, or a' and b' can form a heterocycle optionally containing at least one ~~or more~~ additional heteroatom ~~and~~/or ~~by a~~ heterocycle containing at least one ~~or more~~ heteroatom~~s~~, or R_2 ~~represents a~~ is 

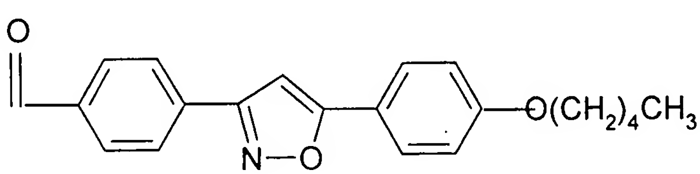
~~radical~~ in which d, e, f and g ~~represent a~~ are hydrogen ~~atom~~ or ~~an~~ alkyl ~~radical containing up~~ of 1 to 8 carbon atoms, f and g can ~~moreover represent an~~ also be acyl ~~radical containing~~ of up to 8 carbon atoms, and e and f can also form a ring optionally containing at least one ~~or more~~ heteroatom~~s~~,

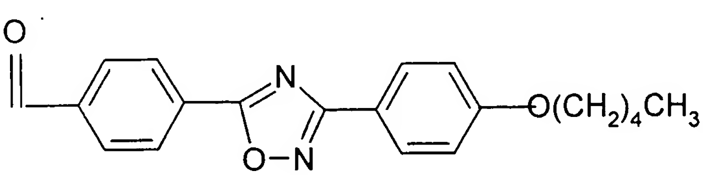
is selected from the group consisting of

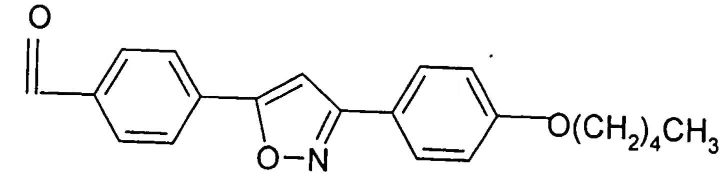
R_3 ~~represents a~~ hydrogen ~~atom~~, ~~a~~ methyl and ~~or~~ hydroxyl, ~~radical~~

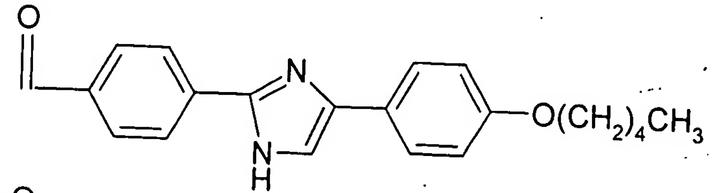
R_4 ~~represents a~~ is hydrogen ~~atom~~ or ~~a~~ hydroxyl, ~~radical~~

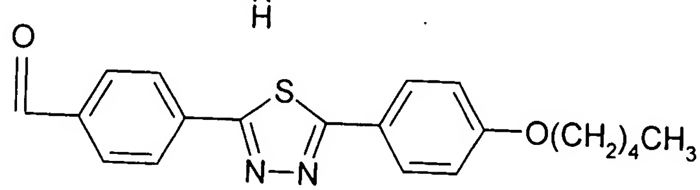
R ~~represents a radical chosen from the following radicals:~~

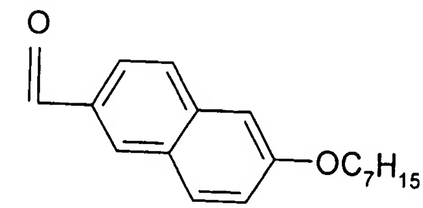


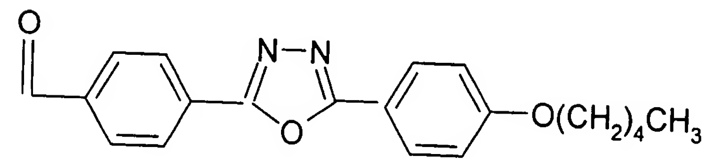


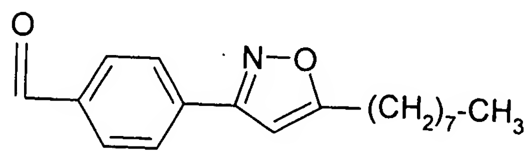


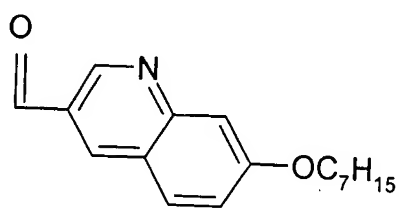




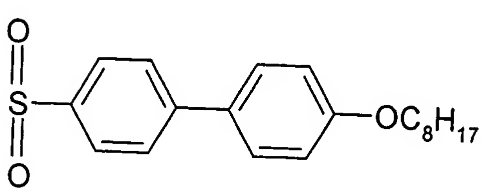








and



)

T is selected from the group consisting of ~~represents a~~ hydrogen a~~tom~~, ~~a~~ methyl ~~radical~~, ~~a~~ $-CH_2CONH_2$, $-CH_2CN$ ~~radical~~, ~~a~~ $-(CH_2)_2NH_2$ and ~~or~~ $-(CH_2)_2Nalk^+X^-$ ~~radical~~, X ~~being a~~ is halogen ~~atom~~ and alk is ~~an~~ alkyl ~~radical containing~~ of up to 8 carbon atoms,

Y is selected from the group consisting of ~~represents a~~ hydrogen a~~tom~~, ~~a~~ hydroxyl, ~~radical or a~~ halogen ~~atom~~ and ~~or an~~ $-OSO_3H$ r~~adical~~ and a ~~or one of the~~ salt~~s~~ thereof ~~of this radical~~,

W is ~~represents a~~ hydrogen a~~tom~~ or ~~an~~ -OH ~~radical~~,

Z is ~~represents a~~ hydrogen a~~tom~~ or ~~a~~ methyl ~~radical~~ and a non-toxic, pharmaceutically acceptable acid ~~as well as the~~ addition salt~~s~~ thereof ~~with acids of the products of formula (I)~~.

2) ~~The~~ A compound~~s~~ of ~~formula (I) defined in~~ claim 1 in which T is ~~represents a~~ hydrogen a~~tom~~.

3) ~~The~~ A compound~~s~~ of f~~ormula (I) defined in~~ claim 1 ~~or 2~~ in which W is ~~represents a~~ hydrogen a~~tom~~.

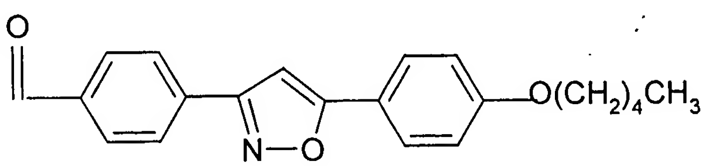
4) ~~The~~ A compound~~s~~ of f~~ormula (I) defined in any one of~~ claim~~s~~ 1 ~~to 3~~, in which Z is ~~represents a~~ methyl ~~radical~~.

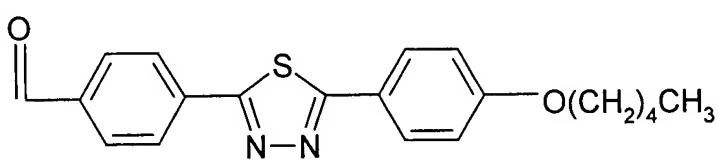
5) ~~The~~ A compound~~s~~ of ~~formula (I) defined in any one of~~ claim~~s~~ 1 ~~to 4~~ in which Y is ~~represents a~~ hydrogen a~~tom~~.

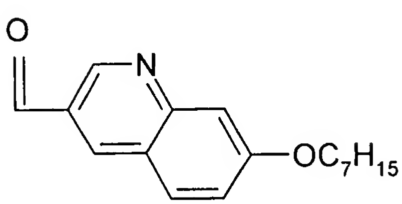
6) ~~The~~ A compound~~s~~ of ~~formula (I) defined in any one of~~ claim~~s~~ 1 ~~to 5~~ in which R_3 is ~~represents a~~ methyl ~~radical~~.

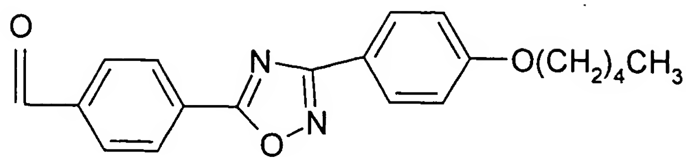
7) ~~The~~ A compound~~s~~ of f~~ormula defined in any one of claims 1 to 6~~ claim 1 in which R_4 is ~~represents a~~ hydroxyl ~~radical~~.

8) ~~The~~ A compound~~s~~ of ~~formula (I) defined in any one of~~ claim~~s~~ 1 ~~to 7~~ in which R is selected from the group consisting of ~~represents a~~



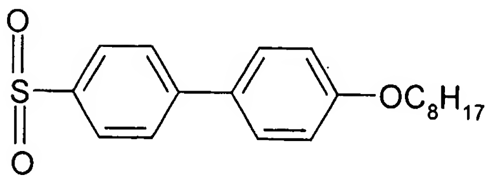






~~radical~~
~~or a~~

and



~~radical~~.

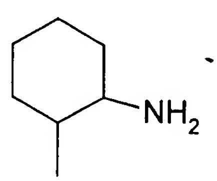
9) ~~The~~ A compound~~s~~ of ~~formula I defined in any one of~~ claim~~s~~ 1 ~~to 8~~ in which R_1 ~~represents a~~ is hydrogen ~~radical~~.

10) ~~The~~ A compound~~s~~ of ~~formula defined in any one of~~ claim~~s~~ 1 ~~to 9~~ in which R_2 ~~represents a~~ is

$(CH_2)_2\ NH_2$

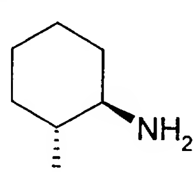
~~radical.~~

11) ~~The~~ A compound~~s~~ of ~~formula I defined in any one of~~ claim~~s~~ 1 ~~to 9~~ in which R_2 ~~represents a~~ is

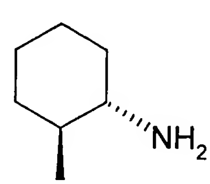


~~radical and in particular the~~

20. A compound of claim 11 wherein R_2 is

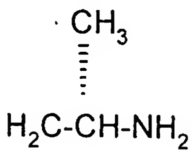
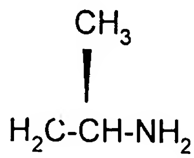
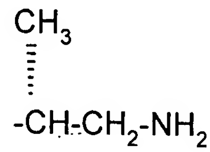


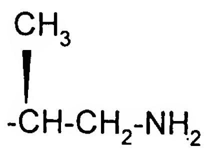
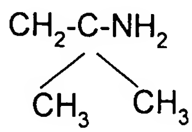
OR ~~and~~



~~radicals~~.

12 ~~11~~) A ~~The~~ compound~~s~~ of ~~formula I defined in any one of~~ claim~~s~~ 1 ~~1 to 9~~ in which R_2 is selected from ~~represents a~~ the group consisting of

, , ,

 and 

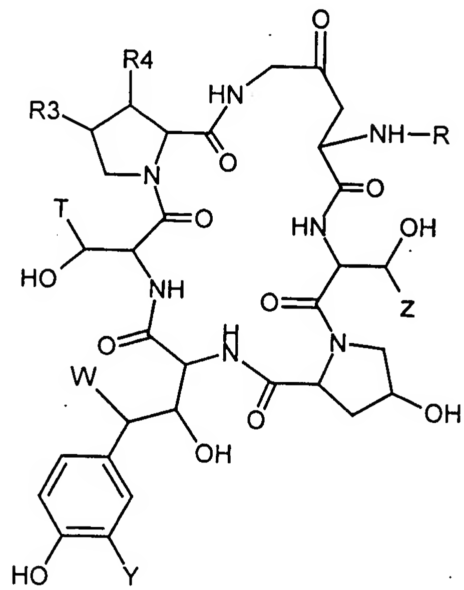
~~radical~~.

13 ~~12~~) A ~~The~~ compound~~s~~ of ~~formula I defined in~~ claim 1 selected from the group consisting of ~~the names of which follow:~~

- 1-[4-[(2-aminoethyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- trans-1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- 1-[4-[(2(S)-aminopropyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-3-isoxazolyl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- 1-[4-[(2-aminoethyl)amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate,
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[5-[4-(pentyloxy)-phenyl]-1,3,4-thiadiazol-2-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate and
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4-[3-[4-

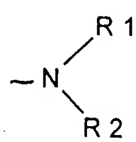
(pentyloxy)-phenyl]-1,2,4-oxadiazol-5-yl]-phenyl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate.

14 ~~13)~~ A ~~p~~process for the preparation of ~~the~~ a compounds of ~~formula (I) defined in any one~~ of claims 1 ~~to 13, characterized in that~~ reacting a compound of the formula ~~(II)~~



(II)

in which R, R_3, R_4, T, Y, W and Z are defined as in claim 1 ~~retain their previous meaning, is subjected to the action of~~ with an amine or of an amine derivative capable of introducing

~~the~~  ~~radical~~ in which R1 and R2 are defined as in claim 1 ~~retain their previous meaning~~ and optionally then with ~~if desired to the action of~~ a reducing agent,

and/or ~~of~~ a functionalization agent of the amine,

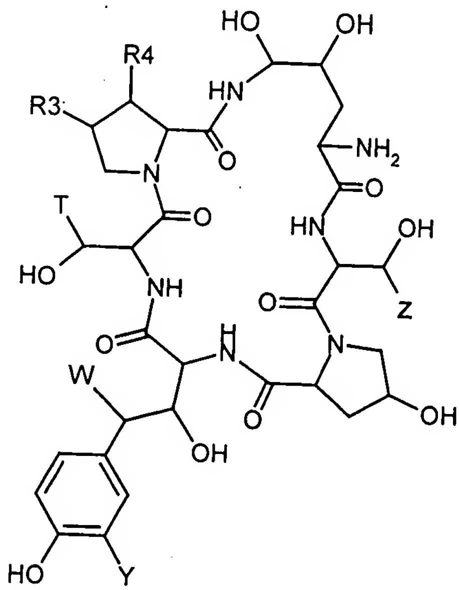
and/or ~~of~~ an acid ~~in order~~ to form the salt of the product ~~obtained~~ of claim 1,

and/or ~~of~~ a separation agent of the different isomers obtained.

~~and in this way the compound of formula (I) as defined in claim 1 is obtained.~~

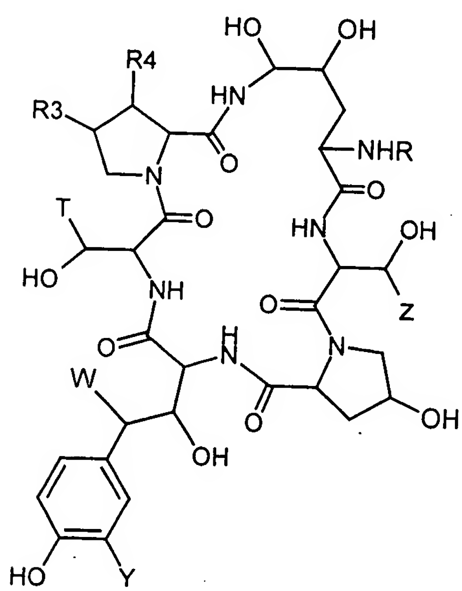
15 ~~15)~~ ~~As new chemical products,~~ A ~~the~~ compound~~s~~ of the formula (insert (II)) wherein R, R3, R4, T, Y, W and Z are defined as in claim ~~defined in claim 14.~~

16) A ~~p~~Process ~~according to~~ of claim 14 ~~characterized in that~~ wherein a compound of the formula ~~(III)~~



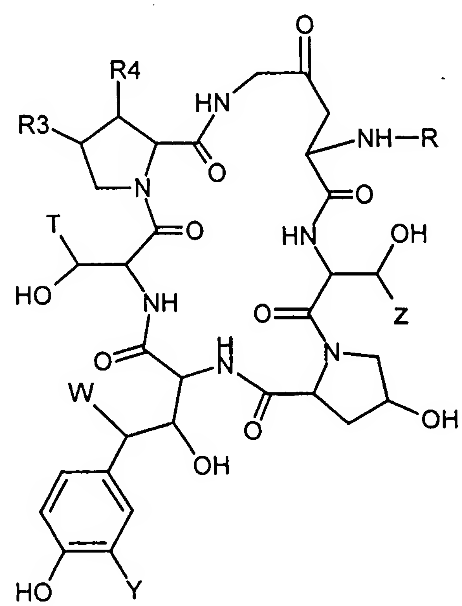
(III)

R_3, R_4, T, W, Y and Z are defined as in claim 14 ~~in which the different substituents retain their previous meaning~~ is ~~subjected to the action of~~ reacted with an agent capable of replacing $-NH_2$ by $-NHR$, R being defined as in claim 14 ~~retaining its previous meaning in order~~ to obtain ~~the~~ a compound of the formula ~~(IV)~~



(IV)

~~which is subjected to the action of~~ reacting the said compound with trimethylsilyl iodide ~~in order~~ to obtain the corresponding compound of the formula ~~(II)~~



(II)

17) As new chemical products the compounds of formula III and IV defined in claim 16.

18) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 13, as well as their addition salts with acids.

19) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 13 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.